Effect of Acupuncture on Smoking Cessation and Chronic Neck and Shoulder Pain

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To my dear parents

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PREFACE

Traditional Chinese Medicine (TCM) came into my life in an early age. My mother, a physiologist, was sent to the countryside, as were many of the academics at the end of 1960s. In the poor countryside, she became an after-work "bare-foot doctor", and used acupuncture to help the farmers in villages. I was so proud of my mother, and at the same time fascinated and inspired by the magic effects of those small silver needles.

After several years studying and working at university in Beijing, I came to Norway in the middle of the 1980s, and finished a master's degree (Cand. Scient.) in physiology and worked with related research projects. Nurtured by science and wisdom from both East and West, I have not just enriched my knowledge, but also given possibilities to meet challenges. One of the most interesting challenges is how to combine the best of the Eastern and Western medical traditions to improve healthcare for people.

At the time, a Norwegian would stare at me and wonder how someone with a headache is treated by acupuncture. One of my first patients in 1992 came to me just to look at the needles. We all should be grateful to the Norwegian Research Council for its pioneering program "Projects in alternative medicine". This initiative opened the way for research on acupuncture in Norway, and gave me a real chance to study evidence based acupuncture which is necessary to introduce ancient acupuncture as a medical treatment in the present world.

I have for a while been lost with too many "divisions" in my life. Growing up in China and living in Norway, two different cultures, traditions and languages, all these divided my body and mind. In my profession, writing literature and scientific research are dividing my thinking and time.

I have used more than 10 years to learn that an individual might indeed exist in two different worlds at the same time. I have tried to extract the best of the two worlds, and re-construct my

own spirit. I have described this discovery in the postscript of my poem collection "Butterfly Mist" of 2002.

It took me more than 10 years to obtain the PhD degree, and this process has helped me out of another puzzle. The impulsive and fantasy thinking of writing fiction, and the rigorous attitude in scientific research are very different, but can co-exist in the same mind. Emotional expression or progressive reasoning, they all aim to discover the "truth" of our life.

In these long years of PhD-study, how many times I experienced doubt, hesitation, disappointment and loneliness. Those moments when my hands became wet from nervousness, those sleepless nights wandering on the edge of giving up, and finally the desire of discovering "truth" overcame all the other thoughts and lures. I kept on going until today. The outcome of this book marks the end of my ten year "long march". My tears of joy and happiness are going to clean up the next start – in literature or science.

He Dong

Oslo, 28th January 2008

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My close friends Ellen Sekkelsen, Marianne Elisabeth Lien, and Anne Bøe have companied my thoughts during the study. Their efforts to push me forward while I was confused will never be forgotten in my life.

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In China, the famous TCM-doctor Zhang Bao Jian with family medical skill accumulated down seven generations, has been my private instructor for 20 years. In addition to his abundant and exclusive theories and practices of Traditional Chinese Medicine, he taught me how to be a really good doctor. This is what I am mostly grateful for. Also thanks to Chief-doctor Yu Fa Jing and Professor Luo He Chun for good advice and discussion on my study.

Many thanks for the financial support received for this research from the Norwegian Research Council and University of Oslo.

My dear friend, more like a sister, Dr Yi Fei, with her love and friendship since our childhood, took care of and encouraged me, and as well her husband Philip Heathcote who together helped me with the technicalities of this documentation.

The thoughtful suggestion for the thesis from my brother Dr He Yi is also appreciated.

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He Dong

Oslo, 6th March 2008

LIST of PAPERS

This thesis is based on the following papers:

I. He D, Berg JE, Høstmark AT. Effects of acupuncture on smoking cessation or reduction for motivated smokers. Prev Med 1997;26:208-214

II. He D, Medbø JI, Høstmark AT. Effect of acupuncture on smoking cessation or reduction: An 8-month and 5-year follow-up study. Prev Med 2001; 33:364-372

III. He D, Veiersted KB, Høstmark AT, Medbø JI. Effect of acupuncture treatment on chronic neck and shoulder pain in sedentary female workers: a 6-month and 3-year follow-up study. Pain 2004; 109:299-307

IV. He D, Høstmark AT, Veiersted KB, Medbø JI. Effect of intensive acupunctur on pain-related social and psychological variables for women with chronic neck and shoulder pain – an RCT with six month and three year follow-up. Acupunct Med 2005; 23(2):52-61

SUMMARY

Tobacco smoking, and chronic neck and shoulder pain are major public health problems in the modern society, and both lack effective treatments. This thesis presents two trials focusing on acupuncture as a treatment for these two problems.

Objectives

Study A was undertaken to examine the effects of acupuncture on smoking reduction and cessation, and to examine whether some 'real' acupoints are more effective than 'sham' acupoints for smoking cessation. An additional aim was to examine whether acupuncture treatment can have a long-term effect on smoking withdrawal.

Study B was undertaken to examine whether acupuncture might have a positive influence on chronic pain in the neck and shoulders. Since there might be many 'psychological' problems accompanying chronic pain, the thesis also examined to what extent acupuncture might improve some of these problems, such as headache, quality of sleep, and depression. An additional aim was to investigate whether possible positive effects of acupuncture are long-lasting.

Methods

In Study A, 46 healthy men and women (39±9 years old, mean±SD), who smoked 20±6 cigarettes daily volunteered to participate. The subjects were randomly assigned to a test group (TG) or a control group (CG). Acupuncture was applied at six sessions during three weeks either at anti-smoking acupoints (TG) or at acupoints assumed to have no effect for smoking cessation (CG). Blood samples for measuring variables related to smoking, i.e. serum cotinine and serum thiocyanate, were taken before the first, after the last one and 8 months after the last treatments. Each subject filled in questionnaires about their smoking habits and attitudes at the same occasions, and again 5 years after the last acupuncture treatment.

In Study B, 24 female office workers (47±9 years old, mean±SD), who had neck and shoulder pains for 12±9 years, were randomly assigned to a test group (TG) or a control group (CG). Acupuncture treatment was applied ten times during 3–4 weeks either at presumed anti-pain acupoints (TG) or at placebo acupoints (CG). A physician measured the pressure pain threshold (PPT) in the neck and shoulder region with algometry before the first treatment, just after the last one, and 6 months after the treatments. Questionnaires on muscle pain, headache and on changes in social and psychological variables were completed at the same occasions and again 3 years after the last acupuncture treatment.

Main results

In Study A, altogether 31% of subjects in TG had quit smoking completely at the end of the treatment, against none in CG. The subjects' reported cigarette consumption fell on average by 14 (TG) and 7 cigarettes (CG) daily during the treatment period. For both groups the values rose on average by 5–7 cigarettes smoke per day at 8 months follow-up, and there was no systematic change thereafter. Consequently, TG showed a maintained reduction in smoking; no lasting effect was seen for CG. The TG reported that the taste of tobacco was worse than before the treatments, and also the desire to smoke fell. For TG the serum cotinine concentration decreased, and the values correlated with the reported cigarette consumption.

In Study B, the subjects' reported intensity and frequency of pain, and the degree of headache fell more for TG than for CG during the treatments. At 3 years follow up TG still reported less pain than before the acupuncture treatments, contrary to what CG did. For TG the value of PPT of some muscles increased during the treatments and remained higher 6 months after the treatments, which contrasts the situation for CG. The pain-related activity impairment at work was significantly less in the TG than the CG by the end of treatment and 3 years later. The TG showed further improvements in most pain-related variables, i.e. quality of sleep, anxiety, depression and satisfaction with life right after the treatments, at 6 months and 3 years follow-ups, and was again significantly different from the CG.

Conclusions

Appropriate acupuncture may help motivated smokers to reduce their smoking, or even quit smoking completely, and the effect may last for at least 5 years. Different acupoints appear to have different effects for smoking withdrawal. Acupuncture may affect the subjects' smoking by reducing their taste of tobacco and their desire to smoke.

Appropriate acupuncture may reduce chronic pain in the neck and shoulders and related headache, and may also improve the activity at work and several relevant social and psychological variables in people with chronic pain. The effect may last for at least three years. Hypothetically, acupuncture may reduce chronic pain by breaking the vicious circles involved e.g. pain, depression and reduced activities.

DEFINITIONS and ABBREVIATIONS

DEFINITIONS

1. Acupuncture
   - insertion of fine needles into the skin of the body at specific points, in order to promote health and restore proper function of the body

2. Electroacupuncture
   - electrical stimulations to achieve the effect of acupuncture, obtained either by connecting electrodes with the needles inserted into acupoints, or by applying the electrodes directly on acupoints of the skin

3. Acupressure
   - treatment completed by giving pressure on acupoints by a finger, probe or herbal seed to achieve the acupuncture effect; most of the acupressures are carried out without penetrating the skin

4. Acupoint = acupuncture point
   - the site on the surface of the body to which Qi of the organ, meridian or collateral flows gathered; an acupoint has a surface area of 1-5 mm^2, and most of the acupoints are situated in surface depressions along the cleavage between muscles

5. Ear acupuncture
   - acupuncture treatment given on the external ear

6. Sham acupuncture treatment
   - in the thesis: acupuncture applied at sites other than those defined as acupoints, or acupoints assumed without specific relation to the condition under treatment.

7. Placebo acupuncture treatment
   - in the thesis: the control group of the study received a treatment where the needle did not penetrate the skin, or the electro-acupuncture device was disconnected

8. Qi

   - according to the theory of TCM, Qi is the vital energy and life force of the body, flowing through all living things, and influencing health on physical, mental, emotional and spiritual levels

9. De Qi

   - "De" means "to get or receive" in Chinese. De Qi (i.e. to get internal body energy) is a subjective sensation by the patient receiving acupuncture treatment. The sensation is described as numbness, heaviness, press, soreness, heat or distension, when the needle is inserted and retained in the acupuncture points. A skilled acupuncturist can insert the needle to gain De Qi at an acupoint, and also achieve the sensation along the line of the meridian of the patient

10. Tonifying manual needling

    - a quick insertion of the needle in the direction of Qi-flow of the meridian, followed by a gentle manipulation and slow withdrawal, in order to supplement and strengthen Qi

11. Sedating manual needling

    - a slow insertion of the needle opposite the direction of Qi-flow of the meridian, followed by a vigorous manipulation and quick withdrawal, in order to drain and eliminate the excessive Qi

12. Quantifying the taste of tobacco

    - in this thesis, the taste when smoking was measured by a 100 mm visual analogue scale, where the point at 0 mm was defined as "the worst taste of tobacco" and the point at 100 mm "the best taste of tobacco"

13. Quantifying the desire to smoke

    - in this thesis, the desire of smoking was measured by a 100 mm visual analogue scale, where the point at 0 mm was defined as "the lowest desire to smoke" and the point at 100 mm "the highest desire to smoke"

14. Trigger point

    - a focus of irritability in a tissue that, when compressed, is locally tender and, if sufficiently hypersensitive, gives rise to referred pain and tenderness

15. Double-blind experiment

    - an experiment where the subjects both in the group receiving real treatment and in the placebo group do not know whether they are getting real treatment or placebo, and the researchers administering placebo and real treatment are also unaware of which group is receiving which treatment.

16. Single-blind experiment

    - the subjects do not know whether they are receiving real or placebo treatment, or the researcher makes his observations without knowing whether the subject is in the treatment or control group

17. Validation of a measurement

    - assessing if a measurement truly reflects what it is intended to measure

18. Bias

    - any trend in the collection, analysis, interpretation, publication, or review of data which can lead to conclusions that are systematically different from the truth

ABBREVIATIONS

1.	CAM	Complementary and Alternative Medicine
2.	CG	The control group in the thesis
3.	NRT	Nicotine Replacement Therapy
4.	P_b	Level of statistical significance between the two groups
5.	PPT	Pressure Pain Threshold
6.	P_w	Level of statistical significance within a group
7.	RCT	Randomized Controlled Trial
8.	TBARS	Thiobarbituric Acid-Reacting Substances, a measure of lipid peroxidation
9.	TCM	Traditional Chinese Medicine
10.	TG	The test group in the thesis
11.	VAS	Visual Analogue Scale

1 INTRODUCTION and BACKGROUND

Who knows others is wise.

Who knows the self is enlightened.

Lao Zi, *Dao De Jing*

1.1 Brief comment on Traditional Chinese Medicine

The existence of Traditional Chinese Medicine (TCM) can in written form be traced as far back as 3000 years. It is based upon classical Chinese philosophy and the practice of clinical medicine (1). One of the earliest textbook on TCM is written by *Huang Di Nei Jing* (The Yellow Emperor's Canon of Chinese Medicine) finished in the 2nd century BC. The book comprises 162 chapters presenting the fundamental principles of TCM, e.g. the Yin-Yang theory, the five elements, the Zang-Fu theory and the Jing-Luo (Meridian) system of the body (2).

The philosophical basis of TCM is that the human body should be regarded as an integral part of nature, continuously in a state of intensive interaction with the environment. Nature itself is seen as continuously developing and changing. Therefore, medicine and the art of healing are directed towards maintaining the body's balance, both internally and as related to the external world.

1.1.1 Main principles of TCM

1.1.1.1 Yin-Yang; Zang-Fu

The concept of Yin and Yang is based on the philosophical construct of two polar complements that represent the two parts of all things. Yin and Yang are opposite, complementary, and in continuous, reciprocal change to each other. The concepts are used to describe how things function in relation to each other and to the universe. Chinese medical theory believes that, when the energy of Yin and Yang are balanced in the human body, this will bring good health. If one of the energies is dominating over the other, this constellation will produce imbalance and disorders. The purpose of all kinds of treatment is to maintain the balance between Yin and Yang, thereby restoring health.

In TCM, Zang-Fu is the general term for the organs of the human body. Zang refers to Yin organs and includes heart, pericardium, liver, spleen, lung, kidney, while Fu refers to Yang organs and includes small intestine, large intestine, gall bladder, urinary bladder, stomach and San Jiao or "Triple Energizer", i.e. a functional but not anatomical organ in TCM. The twelve organs are also classified according to their function, as well as their ability to manufacture and store different essential substance, e.g. Qi, blood (Zang organs), or to digest food and absorb the ingested substances, and excrete waste (Fu organs). Furthermore, the organs are divided into six related pairs, where each pair includes one Zang (Yin) and one Fu (Yang), e.g. kidney vs. urinary bladder; heart vs. small intestine.

1.1.1.2 Qi, Jing-Luo system and acupoints

According to TCM, Qi is the vital energy and life force that flows through all living things, influencing health at physical, mental, emotional and spiritual levels. Any imbalance of Qi, e.g. deficiency, excess or blockage of Qi, is thought to cause disorders.

In human beings, Qi is thought to flow through the body along the specific Jing-Luos system, usually called meridians in English translation (as meridian on the globe, see Figure 1). The main system of Jing-Luo was completed in *Huang Di Nei Jing* and is a central part in the theory of TCM, especially in acupuncture therapy (2, 3).

The Jing-Luo system consists collectively of 12 main meridians (including 12 meridian branches, 12 meridian tendons, 12 skin areas and 12 collaterals), and eight extra meridians (4, 5). The 12 main meridians are named after the Zang-Fu systems in TCM. Each meridian is connected to the corresponding organ: Thus, the Yin meridians are linked to the lung, spleen, heart, kidney, pericardium, and liver, and the Yang meridians to the large intestine, stomach, small intestine, urinary bladder, San Jiao and gall bladder. The six Yin meridians run on the medial and ventral side of the body, while the six Yang meridians run laterally or on the dorsal side. The eight extra meridians are named "functional" in the TCM system, e.g. the Du (GV), and Yinqiao meridian (see Figure 1).

The 12 meridians of the paired organs run parallel to one another and are connected through eight extra meridians, and also through the Lo collaterals at the periphery, so as to make up a continuous net-system for the flow of Qi in the body (Figure 1). Moreover, each of the 12 main meridians is linked, and belongs functionally to specific, corresponding organs. Thus, the main meridians are connected by means of its branches and collaterals to other meridians, so as to build up an extensive, functional interaction between organs, meridians, and indeed the whole body.

Along these meridians lies the major part of acupuncture points/acupoints, which are believed to be the sites involved in most of Qi convergence and transfer in the body. In the famous classical textbook of acupuncture and moxibustion *Zhen Jiu Jia Yi Jing* (The Comprehensive Manual of Acupuncture and Moxibustion), written by Huang Fu Mi on 282 AD, a total of 649 acupoints were defined and classified accurately on the human body (6, 7). This fundamental work has been one of the most important references for acupoints in the education and practice of TCM up to the present.

When Qi flows freely in the Jin-Luo system, the person is healthy and well balanced. If Qi is blocked, the person may become physically or/and mentally ill. Acupuncture treats disorders by insertion of needles into acupoints in order to influence the unbalanced flow of Qi, thereby restoring the normal balance and proper function of the body. For example, if Qi is weak; acupoints can be stimulated to increase it.

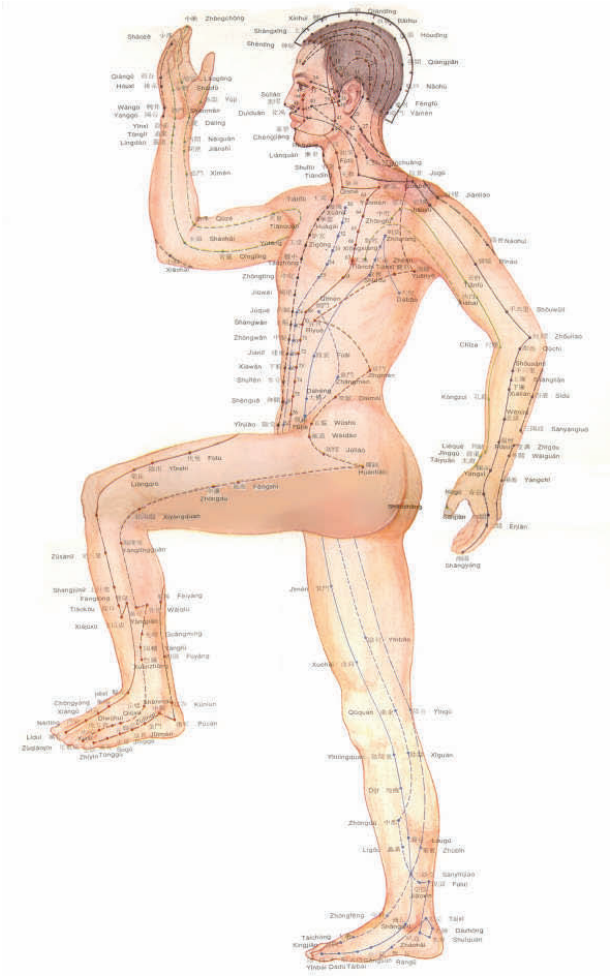


Figure 1. The main meridians of Jing-Luo system in TCM (8)

1.1.2 Suggested pathogenesis of tobacco smoking, according to TCM

The main target organ for a tobacco smoker is the lung. In TCM, the lung is one of the most important organs responsible for the transformation and distribution of Qi. The lung converts inspired fresh air into Zhong Qi, i.e. the Qi which is facilitating the function of other organs (9, 10). Cigarette smoking disturbs this process. Inspiring smoke and nicotine, defined by Chinese medicine as Zhuo Qi (impure air), blocks the clear passage of descending Qi. The functional impairment caused by disturbing the purification and descent of Qi leads to a

deficiency of lung-Qi; hence, several disorders can develop, such as cough, allergy, bronchitis, asthma and even lung cancer (11, 12).

Lung is also regarded as the most sensitive organ to heat and cold (10, 11). Smoking can additionally bring extra "perverse heat and dry" into the respiration system and convert it to internal *fire*, which is regarded as one of the most harmful energies to the lung, because it tends to exhaust the lung Qi. Impaired lung function furthermore leads to unbalanced energy in the large intestine, spleen and kidney, and may cause severe diseases (10).

Both classical Chinese acupuncture and ear acupuncture can be used to counteract nicotine addiction. The aim of treatment is to eliminate heat, pacify passage of Tai Qi and then replenish lung Qi (9, 10). The acupoints on lung meridian and acupoint "shenmen" are the most common ones utilized for smoking cessation (12-14). The details of acupuncture treatment will be discussed more in the Method Chapter.

1.1.3 Suggested pathogenesis of chronic neck and shoulder pain, according to TCM

Generally speaking, the reason for pain is blocking the flow of Qi in Jing-Luo system, as expressed by the well known phrase in TCM: "Bu Tong Ze Tong" (i.e. Blockage in flow of Qi causes pain). Chronic neck and shoulder pain in Chinese medicine belongs to "Bi syndrome", which means obstruction of Qi and blood (15-17). The pathogenesis of Bi syndrome was described already in *Huang Di Nei Jing* several thousand years ago: "The invasion of wind, cold and damp leads to Bi syndrome (18)".

Diagnosis of muscle disorders in Western terms often addresses a local focus, while in TCM the problem is considered from a more systemic point of view. The perverse energies "wind", "cold" and "damp" can destroy the balance of Qi circulation in the body, e.g. the external climate and strong wind can affect gall bladder and urinary bladder meridians. If the invasion of wind influences superficial at acupoint Fengchi (GB 20), it can give rise to pain and stiffness in the cervical spine, and sometimes headache. If the wind penetrates into the deeper level of the meridian, the patient may also present with a stiff painful shoulder.

One of the most famous ancient doctors of TCM, Zhang Zhong Jing (living 150-219), pointed out that “wind” and “cold” can invade the urinary bladder meridian and then cause recurrent pain in the neck and upper part of the body (19, 20). Some authors consider that prolonged sitting or reading can also cause blockage of Qi in the urinary bladder meridian, and also lead to neck and shoulder pain (17, 21).

Many different kinds of techniques in TCM can be used to treat chronic neck and should pain, such as acupuncture, moxibustion, Tuina (Chinese medical massage) and herbal medicine. Focusing on acupuncture, the purpose of treatment is to eliminate the invading pathogens, e.g. “wind”, “cold” and “damp”, and to restore the balance of Qi in the blocked meridians. Clearly, the philosophy and pathogenesis of TCM is very different from that of modern Western medicine. More treatment details will be discussed further in the Method Chapter.

1.2 Approaches to quit smoking

1.2.1 Brief problem statement and overview of methods used for treatment

Tobacco smoking is a leading risk factor for premature disability and mortality from several causes. The World Health Organization estimates tobacco use as the major preventable cause of adult death, and about 5 million deaths worldwide each year (8.8% of all deaths annually) are attributed to smoking (22). Half of tobacco users will die of a tobacco-related disease. The leading causes of death from smoking are cardiovascular disease, chronic obstructive pulmonary disease and lung cancer (23-25).

Knowing the harm of tobacco smoking, 78% of Norwegian smokers (i.e. 25% of the adult Norwegian population) made an effort to quit, and half of them had tried to stop smoking more than three times (26, 27). On average, people who smoke try to quit 12 times or more before they succeed (28). It seems that many smokers need assistance for smoking withdrawal.

Over the past half century, more than 300 smoking cessation programs have been reported since the first public tobacco withdrawal clinic was established in Stockholm in 1955 (29). The most familiar approaches among them are medication such as nicotine replacement

therapy (NRT) (30, 31) and bupropion sustained release (32, 33), as well as behavioural techniques, such as self-monitoring, and group behaviour therapy (29, 34). In a review article based on 633 studies of the most available interventions for smoking cessation and a sample size of 71,806 subjects, Viswesvaran and Schmidt (35) concluded that the average observed success rate across all methods was approximately 19%, and 6.4% for placebo controls.

Unfortunately, for all conventional procedures used to treat tobacco dependence there is a relatively high relapse rate. Although the effectiveness of Nicotine Replacement Therapy (NRT, i.e. a way of getting nicotine into the blood vessels without smoking) on smoking cessation has widely been demonstrated (overall efficacy of NRT treatment was 10.7%), the overall relapse rate was 30% according to a review of 12 placebo-controlled trials, with follow-ups ranging from 2-8 years (36). Moreover, the relapse rate of NRT treatment increased more rapidly in women than in men (30). Some researchers consider that people who relapse should be offered more than one medication, higher doses, or various treatment combinations (37). In a Cochrane Database Systematic Review on group behaviour therapy programmes for tobacco withdrawal (34), the authors analyzed 55 trials and concluded that group therapy is better than individual treatment for helping people to stop smoking. In another meta-analysis review of 48 studies on smoking cessation in teen-agers (38), the average treatment quit rate under the program conditions was 9.1% versus 6.2% under controls. Motivation-enhanced and cognitive-behavioural programs obtained the best results.

Because of the limitations of conventional techniques for smoking cessation, i.e. relatively low success rate, quick relapse, and unpleasant withdrawal symptoms, many smokers have searched for help in complementary and alternative medicine (CAM). Thus, in a recent survey among 1,175 smokers, Sood and colleagues (39) found that 27% of the subjects used CAM as an aid for tobacco cessation. A total of 67% of the subjects reported interest in future use of CAM for smoking cessation, and 20% of the subjects among them reported that the conventional treatments failed to help them to quit smoking.

A number of approaches in CAM have been carried out as an aid to stop smoking. Hernandez-Reif and colleagues (40) found out that a self massage group smoked fewer cigarettes, revealed lower anxiety scores and had lower smoking cravings than controls on a behavioural program. Using high frequency repetitive transcranial magnetic stimulation (41), a significant

decrease in cigarette consumption was achieved. The effect was observed only in an active stimulation group, but not in a sham control group. A sustained quitting rate was reported using relaxation imagery (42), by treating with herbal tea preparations (43), as well as by acupuncture (more in the next 1.2.2).

On the other hand, there was considerable heterogeneity between the results obtained in nine individual studies using hypnosis for smoking cessation. Thus, there are conflicting results as regards the effectiveness of hypnotherapy compared to giving advice, or no treatment (44). There seems to be insufficient evidence to draw any conclusion on the efficacy of the treatments referred to above as regards tobacco withdrawal (45), in spite of the fact that the question of their possible positive effects on smoking cessation has been addressed in several trials using many CAM techniques.

1.2.2 Acupuncture for smoking cessation

In the early 1970s, Wen, a well-known Hong Kong neurosurgeon, reported that electro-acupuncture produced relief of the withdrawal symptoms of opium addiction in patients with post surgical pain (46). Since then, various acupuncture methods have been studied as a treatment regime for helping people to quit smoking, i.e. classical Chinese acupuncture and ear acupuncture; both techniques can be applied with or without electrical stimulation on acupoints. Some researchers used laser ear acupuncture or indwelling ear acupuncture, in which small needles shaped like thumb-tacks were inserted into the acupoints.

Using laser ear acupuncture on 85 patients, Zalesskiy et al. (47) reported that 71% of heavy smoking elderly patients quit smoking completely after treatment for two weeks. Fuller (48) claimed that 95% of 194 patients stopped smoking after three ear electroacupuncture sessions. Follow-ups showed an abstinence rate of 41% after 6 months, and 30% after 2 years. Similar results have been obtained in other studies using ear electro-acupuncture. Thus, Ballal and Khawaji (49) reported a 50% cessation rate, and 45.5% of the treated subjects were able to reduce tobacco use to 5 cigarettes per day or less. Waite and Clough (50) found cessation of smoking in 12.5% of the treated subjects six months after ear electroacupuncture, compared with none of the subjects in the placebo group. Their results were confirmed by measuring of urinary cotinine excretion.

A success rate of 88% was reported immediately after using indwelling ear acupuncture in 339 smokers, and the rate of relapse was 31% after two years follow-up (51). In another study, using 4 weeks' indwelling ear needle pressure, the cessation rate was 19% at one year follow-up (52). Applying a combination of ear acupuncture and ear acupressure, Xu et al. (53) treated 100 smokers and observed a cessation rate of 30% at 6 months follow-up. In addition, there are several uncontrolled clinical studies in China in which different acupuncture techniques have been combined to treat smokers. In these latter studies, the reported success rates varied from 55% to 100% as regards smoking withdrawal (54-56).

Some studies have been carried out to evaluate the effect of acupuncture as compared with conventional anti-smoking therapies. Thus, Hackett and co-workers (57) compared the efficacy of four methods for smoking cessation, i.e. ear electroacupuncture, Nicolette, hypnosis and advisory therapy. They concluded that electroacupuncture was the most promising method both immediately after treatment and at 6 and 12 months follow-ups. The superior effect of acupuncture was also validated by physiological measures, i.e. alveolar carbon monoxide concentration as estimated with an Ecolyser instrument. In another approach in the early 1990s, some researchers compared indwelling ear acupuncture with behavioural therapy and waiting-list (no treatment) (58). The results showed that acupuncture was more effective than the other two groups for helping people to stop smoking right after the treatment, but not at 1 and 3 months follow-ups. Using the ear seed acupressure method (Wangbuliuxingzi), Tian and Chu (59) obtained a significantly higher cessation rate (24%) by acupuncture than by advice (1%) at one year follow-up; the result was confirmed by assessing the level of carbon monoxide. Bier et al. (60) observed differences in the effect of acupuncture and education, alone and in combination, on smoking cessation. One month after the treatment, the combined acupuncture and education group had a quit rate of 40%, i.e. twice the rate observed by sham acupuncture and education, and 4 times the quit rate by acupuncture alone. The same group experienced the largest decrease in daily cigarette consumption among the groups ($P = 0.003$). The treatment effect trend persisted at 18 months follow-up, but there was no statistically significant between-groups difference owing to a high drop-out rate.

On the other hand, several studies have reported that both real and sham acupuncture can cause a significant decrease in cigarette consumption, with no difference between real and

sham/placebo acupuncture treatment (61-67). After stimulating the assumed "effective" acupoints for anti-smoking both on body and ear, the cessation rate in one month, three months and six months were 25%, 21% and 8%, but there was no difference as regards cigarette reduction between real and placebo treatment (63). In a cross-over, controlled pilot study (65), there was no significant difference in cigarette consumption between the active and sham groups after individual body acupuncture (not standard) treatment. Similar results were observed by Gillams et al. (61), using indwelling ear acupuncture on patients smoking over 50 cigarettes daily. White and colleagues (66), used ear eletroacupuncture on "Lung" acupoint for the active group and placebo acupoints for the control group. They showed that the rates of cessation two weeks after treatment were 39% and 42% for the active and control groups, respectively. The results were confirmed by measuring the carbon monoxide level in expired air. Cai et al. (67) reported that right after 12 sessions of laser acupuncture treatment, 21% of smokers among high school students managed to quit smoking. Around 80% of them reduced tobacco consumption to about 50%, but there was no significant difference between the active and placebo acupuncture groups.

Georgiou and co-workers carried out a cross-over study for examining the effect of eight different modulations of electrical stimulations of body and placebo acupuncture (68). The subjects receiving active treatment seemed to obtain higher cessation rates than those in the inactive groups, but the difference was not statistically significant. Also, the efficacies on smoking cessation of acupuncture, behaviour therapy, placebo medication and waiting-list have been compared. Cottraux et al. (69) observed that acupuncture had a significantly higher success rate than behaviour therapy 9 and 12 months after the intervention, but there was no difference between acupuncture and placebo medication. The authors concluded that the overall effect was small and non-specific. Similar results were obtained in the study of Clavel-Chapelon et al. (70); i.e. the cessation rate after acupuncture treatment and nicotine gum was significantly higher than in controls at one month and 12 months after the treatment, but there was no difference between these two groups.

1.2.3 Limitations of previous studies on acupuncture used for smoking cessation

The inconsistency of the results in different studies may lead some researchers to question the effect of acupuncture on smoking cessation, both in the short- and long-term. Furthermore,

since some of the studies showed little difference in cessation rates between the "real" and "sham/placebo" acupuncture groups, the existence of specific anti-smoking acupoints has also been questioned. In some systematic reviews, researchers have pointed out that acupuncture may not demonstrate an effect greater than that of placebo, and therefore is ineffective on tobacco withdrawal (29, 71-73).

An important limitation common to most of the studies referred to above (18 among 25 studies) was lack of biochemical validation of outcomes, since only the subjects' self-report were used to assess cigarette consumption. In a recent review article which identified 24 controlled trials on active acupuncture in this field as compared with sham acupuncture, only 6 of them (including the present Study A) estimated the effect on smoking cessation by biochemical testing (73).

Another problem is that the acupuncture treatment given differs between studies both in terms of session duration, frequency and in acupoints used (74). The appropriate acupuncture dose has not been emphasized in the acupuncture research field yet, although it is an essential point of achieving possible effect of acupuncture treatment in TCM. It may be that a true effect requires that a relatively broad and intensive treatment is given, i.e. a treatment combining different techniques and using several acupuncture points (More details are addressed in Discussion Chapter, Section 5.4.1).

The third limitation is that few studies have carried out long-term follow-up, to look at the possible prolonged effect on subjects smoking habits (75).

Finally, there seems to be no studies that measured the subjects' taste of tobacco or their desire to smoke, although there are some studies reporting that some subjects' desire to smoke was smaller, and they felt that tobacco no longer tasted as good as before the acupuncture treatment (47, 48, 57, 65).

1.3 Chronic musculoskeletal pain

1.3.1 Problem statement and brief overview of methods used for treatment

Chronic neck and shoulder pain is a major medical and social problem, especially among women. A recent report showed that in Norway, a frequent work-related health problem is chronic pain in the neck, shoulder and upper back region, affecting 12% and 26 % of Norwegian female workers to severe and moderate levels, respectively (76). In a Swedish population, 18.5% of females and 13.2% of males had neck pain for longer than 6 months (77). A number of epidemiological studies show a life-time prevalence of neck pain around 30% to 71% (78-80). Although the prevalence appears to vary in different nations, the situation is essentially the same, at least in the industrialized countries (81).

Moreover, psychological and psychosocial factors have been shown to be important in musculoskeletal pain generally. Patients with chronic pain often experience pain-related depression, anxiety, loss of mobility, and inhibited ability to carry out work and daily activities (82-85). Depression has been documented to be associated with high levels of self-reported chronic pain, low level of physical and psychosocial functioning and poor response to treatment (86, 87). Psychological variables, such as anxiety and depression, affect biological and behavioural responses which feed back to further negatively promote the emotional response to pain, thereby producing a vicious circle, with disability as a consequence (88). Thus, chronic neck and shoulder pain has not only physical, but also psychological and social effects that can reduce the patient's quality of life.

Neck and back disorders represent one of the most common causes for both short- and long-term sick leave and disability pension (89, 90). In a Norwegian survey of 156,644 subjects taking sick leave for more than two weeks due to musculoskeletal and connective tissue disorders, 20% were attributed to neck and shoulder pain (91). Kjellman and co-authors (92) reported subjects sick-listed with neck and shoulder diagnoses, in a 12-year perspective, experienced more frequent and more long-standing symptoms. Their discomfort had a greater impact on both activities of daily life and self-perceived general health, as compared to those with low back problems. In the 10 years cohort study of Ekenbäck and Hagberg (93), 56% of the women in the group with initially severe neck and shoulder pain reported that they still suffered daily pain 10 years after the onset of their symptoms. Furthermore, 59% of subjects

suffered moderate or severe residual pain. None of the women indicated that they were free from discomfort at the 10 years follow-up. Therefore, the growing magnitude of problems with neck and shoulder pain in the society, and the many socio-economic factors involved, demand that more research should be concentrated on the efficacy of treatment.

There are various treatment options for chronic musculoskeletal pain. Conventional pharmacologic and non-pharmacologic approaches, include physiotherapy, physical treatment, radiotherapy, psychological assessment and behavioural treatment (94). Several systematic reviews have shown that the effectiveness of such conservative interventions is open to question (95, 96).

According to a report from USA, 57% of people with neck pain used CAM in the previous 12 months (97). Over one in three US adults used CAM in the past year, representing about 72 million people (98). In the Scandinavian countries, the prevalence of ever-use of CAM was 34% in Norway, 45% in Denmark, and 49% in Stockholm (99). A recent survey provided direct evidence that in England, 84% of patients suffering from musculoskeletal pain had used at least one CAM treatment for pain relief in the previous year, and 65% of them were current users of CAM (100). Among a wide range of therapies, acupuncture, massage, relaxation and chiropractic care are applied most commonly. Despite the high popularity of CAM, there is little Western scientific evidence to prove a superior effect of most of the techniques used in CAM as compared with conventional or placebo treatments (101).

1.3.2 Acupuncture for chronic musculoskeletal pain

1.3.2.1 Acupuncture for chronic neck and shoulder pain

Since the 70's a great deal of laboratory research has been carried out on the effect of acupuncture for different chronic painful syndromes. In 2002, the World Health Organization (WHO) published a review of all clinical trials through the year 1999 and determined four categories of disorder treated by acupuncture. Acupuncture was reported to be an effective treatment for several disorders of the first category, i.e. chronic pain conditions, such as neck pain, headache, and low back pain etc. (102).

Acupuncture is a commonly used treatment for chronic neck and shoulder pain. In a survey of 500 acupuncture patients in general practice, among a wide variety of conditions, the most common symptom was neck and shoulder pain (19% of all patients) (103). In another random sample in Norway, among 653 responding persons, 19% had undergone acupuncture therapy for their condition, most often for muscular-skeletal pain (104).

Unlike the inconsistent opinions as regards the benefit of acupuncture on tobacco withdrawal, there is now a considerable amount of data supporting the efficacy of acupuncture for chronic pain. But we still meet limitations when comparing the results of various acupuncture studies carried out to reduce chronic pain, due to the large variation in the acupuncture techniques applied, and in the assessment of outcomes. In addition, most of the studies examined only the acupuncture effect on one location, such as neck pain, shoulder pain or low back pain, while very few trials have assessed the influence of acupuncture for chronic neck pain, and at the same time, for shoulder pain.

Nabeta and Kawakita (105) investigated the effect of real and placebo acupuncture for neck and shoulder pain. After 3 classical body acupuncture treatments on 16 trigger points, the real treatment group experienced a significant reduction of pain intensity right after and one day after each treatment, but not one month later. The measures of PPT in their study tended to increase for the real acupuncture group but not for the controls. Another study reported that 65% of subjects experienced significant long-term improvement of chronic neck and shoulder pain, as a result of non-standardized electroacupuncture for maximal treatment of 15 sessions, but the authors did not mention the duration of the follow-up (106).

To assess possible different influences of acupuncture and physiotherapy for chronic neck pain, two studies draw similar conclusions that acupuncture had better effects in 3 weeks to 6 months short-term follow-up; even both treatments reduced the subjects' pain (107, 108). By comparing the effectiveness of acupuncture, massage and sham laser acupuncture, the authors summed up that the acupuncture group had a greater reduction in chronic pain than the massage group, but not greater than sham controls, after five treatments (109). Recently, the results from an RCT using transcutaneous electrical nerve stimulation (TENS) on acupuncture points (i.e. a type of electroacupuncture) and exercise on patients with chronic neck pain

demonstrated that after 12 sessions' treatment, both the TENS and exercise groups had less disability and pain than the control group treated only by infrared irradiation (110).

Several studies have demonstrated that real acupuncture is more effective than sham- or placebo acupuncture in relieving chronic neck pain, while others reported that real and sham acupuncture has the same effect.

Adequate acupuncture can lead to significantly less neck pain as reported by Birch and Jamison (111); they examined the effects of acupuncture applied on real and sham acupoints. In an RCT cross-over study, Irnich and colleagues (112) found out that real acupuncture, after a single session of treatment, is slightly better than placebo laser acupuncture in reducing motion-related neck pain. Using a decommissioned electroacupuncture technique as placebo stimulation, White et al. (113) pointed out that real acupuncture reduced neck pain and produced a statistically significant effect compared with placebo treatment, but the difference between the two groups was only 12%, which authors addressed this difference was not clinically interesting. More recently, a similar placebo technique was applied in another study in which acupuncture was found to be more effective than placebo treatment in reducing pain intensity and medication (114).

In the end of the 90s, some researchers (115) started to use the "sham acupuncture needle", which was designed to make the patient feel puncturing of the skin. By using sham needles for their controls, Kleinhenz et al. (116) reported a significant difference between real and placebo acupuncture as regards relief of chronic pain in athletes.

In contrast to this, for the subjects with neck pain, no difference between classical electroacupuncture and sham acupuncture on pain reduction was reported by Zhu and Polus (117), right after treatment and at 4 months follow-up, although both groups showed significant improvement on the observed variables, e.g. reduce on pain. Others have failed to prove that true acupuncture on 5 body acupoints is more effective on pain reduction than sham treatment (118)

In a recent Cochrane systematic review with reanalysis of 10 RCT on acupuncture for neck disorders (119), it was concluded that there is moderate evidence that acupuncture can relieve pain right after acupuncture treatment better than some sham and inactive treatments. Additionally, as compared with inactive treatment, acupuncture also showed a positive effect at short-term follow-up (from one day to three months).

1.3.2.2 Acupuncture for chronic musculoskeletal pain-related headache

Few studies have reported effects of acupuncture on chronic musculoskeletal pain-related headache. Strauss (120) found that treating subjects with individually adapted acupuncture resulted in an 84% improvement for neck pain-associated headache. Recently, Lü and Shan (121) found that both acupuncture needling techniques (turtle-probing and routine needling) gave significant improvement on cervicogenic headache, while the turtle-probing needling obtained effect more rapidly. By comparing the effect of acupuncture and hypnosis for chronic neck pain-related headache, the authors concluded that both treatments can help reduce headache, while the acupuncture group benefited most among patients with acute musculoskeletal pain, and hypnosis therapy did most for patients with psychogenic pain (122).

In a recent epidemiological study in Germany involving 2022 patients with chronic headache, Melchart and co-workers (123) reported that statistically highly significant and clinically relevant improvement was seen for all clinical outcome measures in all nine diagnostic headache groups. Over a half of the patients experienced a 50% decrease in headache frequency compared to baseline data. Otherwise, there have been several reports confirming the positive effect of acupuncture for different types of headache, such as tension-type headache and migraine (124-126). More details of the studies will not be referred to here since the topic is beyond of the scope of the present thesis.

1.3.2.3 Acupuncture for chronic musculoskeletal pain-related social and psychological variables

Social and psychological factors, such as anxiety, depression, stress and health-related quality of life appear to be very important in the development of chronic pain and disability. Therefore, appropriate treatment of chronic pain should estimate improvement in the patient's

social and psychological variables, as well as in biomedical or biomechanical variables. The benefits of treatment are reflected in a patient's return to more normal life, both at work and in private.

To our knowledge so far, there is no other experiment that has reported the possible effects of acupuncture on chronic neck and shoulder pain-related social and psychological variables. Indeed, only few acupuncture studies for chronic pain have touched this topic, and have just addressed the results as secondary outcomes measures.

In 1980s, Coan (127) described a significant improvement on activity at work for patients in the acupuncture treatment group over the waiting list group. By applying individual body acupuncture for more than 300 patients with chronic pain, Junnila (128, 129) found that 58% of the patients experienced higher working capacity after treatment. In particular, 5% of the patients who were unable to work before treatments returned to work after the acupuncture intervention.

Sator-Katzensschlager and co-workers stated that psychological well-being, physical activity, and quality of sleep were significantly better in patients receiving ear electroacupuncture than manual ear acupuncture in two separate studies, one was dealing with chronic neck pain and another was chronic low back pain (130, 131). Similar improvements were obtained by Carlsson and Sjölund (132), who examined effects of acupuncture on chronic low back pain. They found that acupuncture improved the return to work and the quality of sleep for the subjects both post-treatment and at 6 months follow-up. Their control group who received placebo TENS treatment, showed no such effects. Patients on sick leave may return to full-time job after acupuncture for chronic low back pain. In a recent study of acupuncture for chronic, uncomplicated neck pain (114), the results at one week after the intervention showed greater improvement in the real than in the placebo acupuncture group as regards percentage of incapacity and quality of life, except for the measures of Mental Component Summary of SF-36.

In a prospective cohort survey by Kukuk et al. (133), 249 patients with chronic low back pain or gonarthrosis found that pain tolerance was significantly improved after 10 sessions of classical body acupuncture and at 6 months follow-up. Furthermore, the improvement in pain

tolerance post-treatment correlated with the subjects' depression score and the pain-related physical impairment.

David et al. (107) reported that for chronic neck pain both acupuncture and physiotherapy improved the patients' score on the General Health Questionnaire, which includes measures of anxiety, insomnia, depression and social dysfunction, but there were no differences between the two treatments at 6 weeks and 6 months follow-up. White et al. (113) failed to find any differences on health related well-being variables between a real and a placebo TENS acupuncture group in the study.

1.3.3 Limitations of previous studies on acupuncture for chronic neck and shoulder pain

According to the principle of traditional Chinese acupuncture, treatment should be applied individually, e.g. as regards acupuncture dose and duration, and follow the changes in the patient's symptoms. Unlike traditional Chinese acupuncture, most of the Western acupuncture studies were designed to follow standardized acupuncture protocols. Therefore, it is very important to design appropriate procedures for this latter type of acupuncture treatment, in order to avoid possible false results induced by simplified and inappropriate treatment, e.g. treatment with few acupoints, short duration of session, as well as long interval between each session. Conceivably, some previous negative studies might have used too low dose of acupuncture. This would be an important limitation, especially in studies involving subjects with a chronic pain history.

An important limitation of many previous studies referred to above was the lack of clinical validation (e.g. PPT measurement) on acupuncture for relieving chronic pain.

As mentioned in 1.3.1, some cohort studies have followed their patients with neck and shoulder pain over 10 years (92, 93). The longest acupuncture study in the field was undertaken by Junnila (129), who followed up the subjects for two years after the intervention. Less than 1/3 of the studies referred to above, on acupuncture for chronic musculoskeletal pain, reported their results at 6 months follow-up. In fact, most of the previous studies followed their subjects only few days, and occasionally up to three months.

Thus, in these earlier studies it is not known whether there might have been sustained, long-term effects of their acupuncture for chronic pain.

Furthermore, the fourth limitation in previous studies is the lack of focus upon social and psychological variables associated with chronic pain. In particular, to our knowledge almost no studies have appeared presenting data evaluating possible correlation between reduced neck and shoulder pain and pain-related social factors, such as pain-related activity impairment at work and at home, quality of sleeping, quality of life, and degree of tiredness.

2 OBJECTIVES and APPROACHES

The overall aim of this doctoral dissertation was to investigate whether acupuncture can reduce smoking, and chronic musculoskeletal pain, both constituting major public health problems in the modern society.

The main research questions were:

1. Can acupuncture reduce cigarette smoking?
2. Can acupuncture reduce chronic musculoskeletal pain?
3. Can acupuncture beneficially influence pain-related social and psychological variables in people with chronic musculoskeletal pain?
4. If the answers to questions 1-3 are 'yes', will the effects be long-lasting?

The research questions were tried to be answered by studying:

- - the effects of acupuncture treatment on smoking reduction in moderate smokers motivated to quit smoking (Paper I)
- - whether different acupoints have different effects on smoking reduction (Paper I)
- - the long-term (several years) effects of acupuncture treatment on smoking reduction (Paper II)
- - the effects of acupuncture treatment on chronic pain in the neck and shoulders, and the related headache, in women with such chronic musculoskeletal pain (Paper III)
- - the effects of acupuncture treatment on pain-related social and psychological variables (e.g. activity at work, depression), in women with chronic pain in the neck and shoulders (Paper IV)
- - the long-term (several years) effects of acupuncture treatment on chronic neck and should pain, and pain-related social and psychological variables (Paper III and IV)

3 METHODS

Declare the past, diagnose the present, foretell the future; practice these acts.

As to diseases, make a habit of two things — to help, or at least to do no harm.

Hippocrates, *Epidemics*

3.1 Study design

The thesis consists of two distinct studies, each based on separate materials. Study A intended to examine the influence of acupuncture on smoking cessation. In Study B we wanted to elucidate the effect of acupuncture on chronic pain. Both studies were randomized, single-blinded (partly double-blinded) experimental clinical trials, and both involved a short-term and a long-term follow-up study of the cohorts. Figure 2 outlines the study design. A more detailed description is presented in the following sections.

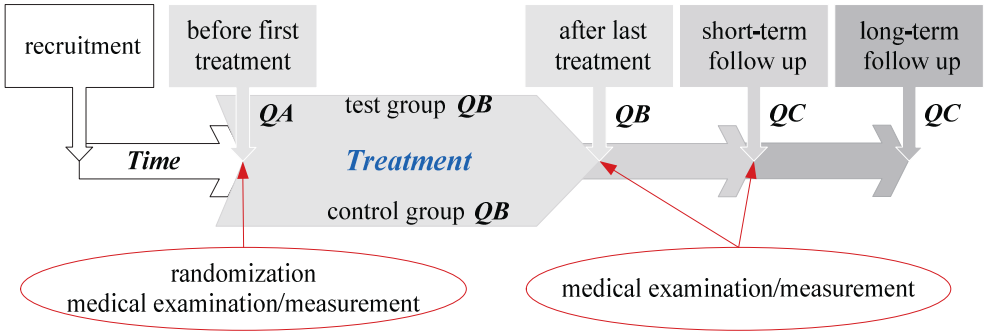


Figure 2. Outline of the study design. QA, QB, QC are different questionnaires, used at various time points of the study. The short-term follow-ups are 8 and 6 months after the last acupuncture treatment for Study A and B, respectively. The long-term follow-ups are 5 and 3 years after the last acupuncture treatment, respectively, for Study A and B.

3.2 The population sample

3.2.1 Study A: Acupuncture for smoking reduction/cessation

Participants in Study A, were recruited from employees for a large company in Oslo, Norway, using an internal advertisement, which was distributed through the company's occupational health office. The same group of subjects participated in the follow-up studies 8 months and 5 years later. The inclusion and exclusion criteria in the study were that the subjects should have at least five years of regular smoking, with an average tobacco consumption of 10–30 cigarettes per day during the last year. It was in addition required that by the time of recruitment and during the period of our treatments, none of the subjects received any other form of treatment for smoking cessation nor any other acupuncture treatment. Persons with diabetes or a history of coronary heart disease were excluded, as well as pregnant and breast feeding women.

3.2.2 Study B: Acupuncture for chronic neck and shoulder pain

The population sample used in Study B was recruited from five companies in Oslo, through the company's occupational physician according to our inclusion criteria. One week before the study the participants received a letter with detailed information about the purpose of the study and treatment procedures. The same cohort participated in the follow-up studies 6

months and 3 years later. The inclusion criteria were that the subjects should be women between 20 and 60 years old, having worked in sedentary occupations or being engaged in light repetitive activities. Their perceived pain in the neck and shoulder region was so severe that the subjects' work and spare time activities were affected, but none of the subjects were on a sick leave at the start of the study. "Chronic pain" was defined as pain being experienced for at least three months during the last year. Persons with diabetes, neurological, rheumatic or other diseases were excluded, as were pregnant and breast feeding women. It was in addition required that none of the subjects received any other form of treatment for chronic pain or any other acupuncture treatment during the period of our treatments.

The subjects for both Study A and B were divided by complete randomization, that is by drawing with replacement, into two groups, referred to as the test group (TG) and the control group (CG). In Paper I-III, the issue of drop-out was discussed in detail and this topic will further be asserted in Discussion 5.1.2.2.

3.3 Acupuncture treatments

3.3.1 Theories and principles of TCM

The acupuncture principle used in Study A was based on the theories in classical TCM. It believes that tobacco smoking causes deficiency of energy (Qi) in the lung brought about by unbalanced energy of "dry" and "heat" into the lung-meridian (11, 12). The acupuncture treatment was therefore concentrated on reducing "lung-fire", and harmonizing the Qi in the lung-meridian.

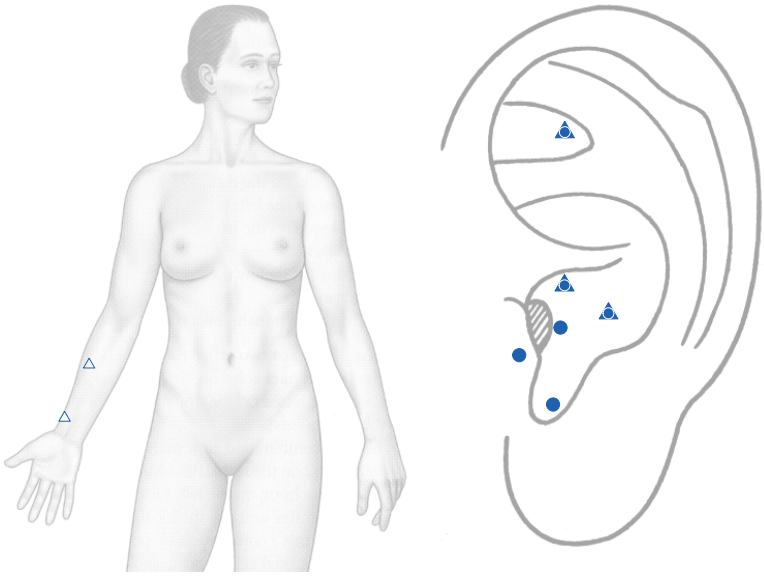
In Study B, chronic pain in the neck and shoulders is here defined as "Bi (obstruction) syndrome" in TCM, and is caused by invasion of pathological cold, wind and damp into the meridians, thereby blocking the flow of Qi. Through this blocking, both physical and mental symptoms would appear in the human body (16-18, 21).

The acupoints chosen on ear and body, in both Study A and B, followed the principles of classical Chinese acupuncture, such as using key acupoints, confluence acupoints, and local acupoints of neck and shoulder region combined with distal acupoints on the affected

meridian in Study B (5, 8, 134-136). The issue will be mentioned further in section Acupuncture dose of Discussion 5.4.1.

3.3.2 Acupuncture treatments used in the present study

Standardized Chinese acupuncture treatments were given to the TG in Study A and B, whereas sham or placebo acupuncture treatment was given to the CG. The treatment was a combination of body electroacupuncture, body or ear acupuncture, and ear acupressure. All acupuncture treatments were carried out in a private acupuncture clinic by Dong He.



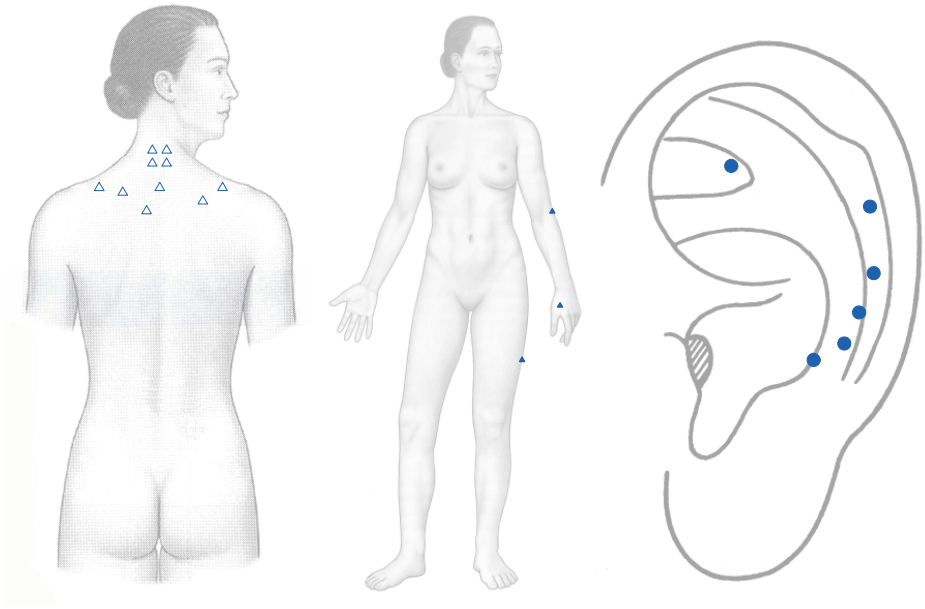
a b

Figure 3. Acupuncture points used for the test group (TG) in Study A. Acupoints used for electroacupuncture (△) are shown in 3a, and acupoints for ear acupuncture (▲) and ear acupressure (●) are shown in 3b. Each treatment was carried out on one side of the body. Image of the body taken from Maciocia (138), image of the ear taken from Li (139)

In Study A, eight acupuncture points (2 body acupoints and 6 ear acupoints) chosen for TG were those acupoints used previously for smoking cessation and are supposed to affect smoking-related organs such as lungs and mouth (Figure 3). The 8 sham points for CG in this

study were those related to the skeletal and muscle systems and are supposed to have no specific effect on organs directly exposed to smoking (13, 134, 137). Electrodes of the electroacupuncture instrument were first placed on two of the body acupoints, with a stimulation period of 20 minutes. Sterile acupuncture needles were inserted in three ear acupoints for 20 minutes, and "rotated" every 5 minutes (134). After the needles were removed, plant seeds (Wangbuliuxingzi, Beijing, China) were placed on six ear acupoints for acupressure. Each seed was kept in place by a piece of 6x6 mm tape until the next session of treatment. The subjects were instructed to press on each of the ear acupoints four times per day, and 100 repeats each time (134). The treatment was carried out on one side of the body each time, twice a week, in a total of six acupuncture sessions over a period of three weeks.

In Study B, altogether 22 points (16 body acupoints and 6 ear acupoints) were selected by several established methods in TCM (Figure 4). The TG received real acupuncture treatment, i.e. using acupoints assumed to have a positive effect on chronic pain in the neck and shoulder region (16, 17, 134, 140). The electrodes of the electroacupuncture instrument were first placed for 30 minutes on the body acupoints of the neck and shoulder area without needles inserted. After the electro-stimulation was started, sterile acupuncture needles were inserted bilaterally in other three body acupoints for 30 minutes and rotated every 5 minutes (134, 140). After the electrodes and needles were removed, plant seeds were placed on six ear acupoints for acupressure until the next treatment. The subjects were instructed to press on each of the ear acupoints, and a series of 100 repeats were carried out four times per day (134).



a b c

Figure 4. Acupuncture points used for the test group (TG) in Study B. Acupoints used for electroacupuncture (△) and body acupuncture (▲) are shown in 4a and 4b respectively. Acupoints used for ear acupressure (●) are shown in 4c. In each treatment, the bilateral acupoints were used for body acupuncture and unilateral acupoints were used for acupressure. Image of the body taken from Maciocia (138, 141), image of the ear taken from Li (139)

The same number of body points (16 body placebo acupoints and 6 ear placebo acupoints) was selected for the CG who received placebo acupuncture treatment. The electroacupuncture was carried out without applying any voltage. However, the instrument did send a short beep at each pulse given, thereby giving an additive signal as if an electric pulse had been sent. The body acupuncture consisted of needles placed to points 10–40 mm distal to the presumed real acupoints, and ear acupressure was placed on points 4–6 mm below to presumed real acupoints. The placebo acupuncture treatment for CG was thus not applied at any known real classical acupuncture points. Each subject received three treatments per week and totally ten sessions over a period of 3–4 weeks. Each treatment lasted 40–45 minutes.

More details of acupuncture treatment are described in Paper I–IV and will be further discussed in the chapter on methodological issues (Discussion 5.1.3 and 5.1.4.3).

3.4 Measurements

3.4.1 Blood sampling and analysis

In order to evaluate possible effects of acupuncture in Study A and B, blood samples were taken before the first acupuncture treatment, one week after the last treatment, and also at the short-term follow-ups (Paper I, II, and III). In Study A the blood samples were collected by the company's occupational nurse and in Study B by a specially trained senior technician, both being unaware of the study's design.

In Study A, the concentration of serum cotinine, serum thiocyanate, serum lipid peroxide (TBARS) and plasma fibrinogen were analyzed at the Central Laboratory, Telemark Central Hospital Porsgrunn, at Ullevål University Hospital, or at the laboratory of Institute for General Practice and Community Medicine, University of Oslo. Cotinine is a primary metabolite of nicotine and therefore considered the most accurate and well-known biochemical variable of smoking status. The cut-off value of cotinine concentration for non-smokers is 71 $\mu g\ L^{-1}$ (142). The concentration of thiocyanate derived from cyanide components in the tobacco smoke is a variable used to assess smoking habits and has been used to estimate the subjects' tobacco consumption (143, 144). Furthermore, plasma fibrinogen and lipid peroxide levels were determined since increased levels of these variables have been observed in smokers (145, 146).

In Study B, we intended to include determination of platelet count, as well as serotonin in plasma and in platelets. Unfortunately, it turned out that there had been technical problems with the analyses. Therefore, no data on the serotonin concentration were obtained.

3.4.2 Questionnaire

As depicted in Figure 2, three questionnaires, A, B and C, were used in the studies. The purpose was to evaluate the effects of the acupuncture treatments and to address other relevant information from the subjects. Questionnaire A (QA), focusing on the personal background and habits, was completed before the first treatment. Questionnaire B (QB) was used to assess possible effects of each acupuncture treatment. And finally, questionnaire C (QC) used for the short- and long-term follow-up examinations.

As mentioned in the Background section, in Study A, we were not only interested in studying the influence of acupuncture on complete smoking cessation, but also on smoking reduction. Moreover, it seemed of interest to measure the subjects' taste for tobacco and their desire to smoke, since this information might serve to elucidate mechanisms behind the effects of acupuncture on smoking behavior. As questionnaires involving these aspects were not found in the literature, we developed a questionnaire that also focused on the subjects' taste of tobacco and the desire to smoke. Both variables were measured on 100 mm VAS-scale. Motivation to stop smoking was assessed using an 10-point Likert scale.

In Study B, the main questionnaire was a slight modification of a standard Nordic questionnaire for the analysis of musculoskeletal symptoms (147) and McGill pain questionnaire (148). The possible changes in pain intensity, pain frequency, and degree of headache were addressed here. Several questions were especially designed for the study. The quality of sleep was measured on a 9-point Likert scale. The frequency of tension and irritability, the degree of tiredness, depression, and satisfaction with life were measured on the 100 mm VAS scale.

3.4.3 Clinical examinations

Study B included a medical examination and a measurement of Pain Pressure Threshold (PPT) by algometry on 28 trigger points located bilaterally on the subjects' neck and shoulders. The details in definition of trigger point and procedure of measurement of PPT were addressed in Paper III. The physician in the study (KBV), who is a specialist in occupational medicine with a PhD on neck and shoulder disorders, carried out the clinical examination. It is pointed out that he was unaware of what kind of acupuncture treatment subjects received until after finishing the study, i.e. after 3 years. It means that this part of the study was double-blinded. The clinical examination took place before the first, after the last, and 6 months after the acupuncture treatment (Paper III).

3.5 Statistics

Most of the statistical analyses were carried out by using the Statistical Package for Social Science (SPSS, version 11.0) and Microsoft Excel 2000 (version 9.0).

The results are presented as mean ± SEM or as individual results unless otherwise stated explicitly. Student's matched-paired univariate tests (within each group) and two-sample t-tests (between TG and CG) were carried out. The level of statistical significance was set to $P \leq 0.05$. Scheffe's and Bonferroni/Dunns post-hoc tests were used for multiple comparisons. Correlations between changes in scores of two parameters were examined by the ordinary Pearson's correlation coefficient (r) or Spearman's rank correlation coefficient (r_S). More details of the statistical methods used are described in the separate papers.

4 RESULTS: SYNOPSIS of PAPERS

To learn without thinking is labour in vain.

To think without learning is desolation.

Confucius, *The Lun Yu*

4.1 Paper I

Effects of acupuncture for smoking cessation or reduction for motivated smokers. ***Prev Med*** 1997; 26:208-214

Objectives To examine the effects of acupuncture treatment for smoking reduction and cessation, and further to examine whether some acupoints are more effective than others for smoking cessation.

Methods Forty-six healthy men and women, 39±9 years old (mean±SD), who had smoked for 23±8 years and consumed 20±6 cigarettes per day, were randomly assigned to a test group (TG) or a control group (CG). Presumed effective anti-smoking acupoints were stimulated (TG), or acupuncture was applied to acupoints considered to have no effect for smoking cessation (CG). Standard acupuncture treatment included electroacupuncture, ear acupuncture and ear acupressure, and was carried out on one side of the body each time, twice a week, in a total of six acupuncture sessions over a period of three weeks. Before each treatment and after

the last treatment, subjects answered questionnaires about their smoking habits and attitudes. The concentrations of serum cotinine, serum thiocyanate, serum peroxides and plasma fibrinogen were measured before the first and after the last treatments.

Results

- The daily cigarette consumption fell during the treatment period in both groups, but the reduction was larger for TG than for CG ($P_b<0.002$).
- 32% of subjects in TG had quit smoking completely at the end of the treatment, against none in CG.
- For TG the concentrations of cotinine and thiocyanate were reduced significantly after the treatment period ($P_w<0.001$), but no such reductions were observed for CG.
- For both groups the taste of tobacco and the desire of smoking fell during the treatment period, but the effect was more pronounced for TG than for CG ($P_b<0.05$; $P_b<0.001$).

Conclusions Acupuncture may help motivated smokers to reduce their smoking or even quit smoking completely. Different acupoints appear to have different effects for smoking cessation and reduction.

4.2 Paper II

Effect of Acupuncture for Smoking Cessation or Reduction: An 8 months and 5 years Follow-up Study. ***Prev Med*** 2001; 33:364-372

Objectives To examine whether acupuncture treatment may have a long-term effect on smoking cessation or reduction.

Methods Forty-six healthy men and women who reported to smoke 20±6 cigarettes per day (mean±SD) were randomly assigned to a test group (TG) or a control group (CG). Standard acupuncture was applied six times during three weeks either at anti-smoking acupoints (TG) or at acupoints assumed to have no effect for smoking cessation (CG). Before each treatment,

after the last one, 8 months and 5 years after the last treatment subjects answered questionnaires about their smoking habits and attitudes. Blood samples for measuring variables related to smoking, i.e. serum cotinine and serum thiocyanate, were taken before the first, after the last and 8 months after acupuncture treatment.

Results

- TG showed a maintained reduction in daily cigarette consumption; no lasting effect was seen for CG (P_b=0.01) at two follow-ups.
- For TG the taste of tobacco was worse than before the treatments (P_w=0.02), and also the desire to smoke fell (P_w<0.001), contrary to what CG did.
- For TG the serum concentration of cotinine maintained reduction 8 months after the last acupuncture treatment (P_w<0.006; P_b<0.05), and the values correlated with their daily cigarette consumption.

Conclusions Acupuncture treatment may help motivated smokers to reduce their smoking, or even quit smoking completely, and the effect may last for at least 5 years. Hypothetically, acupuncture may affect the subjects' smoking by reducing their taste of tobacco and their desire to smoke.

4.3 Paper III

Effect of acupuncture treatment on chronic neck and shoulder pain in sedentary female workers: a 6-month and 3-year follow-up study. ***Pain*** 2004; 109:299-307

Objectives To examine whether acupuncture treatment can reduce chronic pain in the neck and shoulders and related headache, and to examine whether possible effects are long-lasting.

Methods Twenty-four female office workers (47±9 years old, mean±SD) who had neck and shoulder pains for 12±9 years, were examined. Their perceived pain affected their activities at work and at home, but none of the subjects were on a sick leave. The subjects were randomly assigned to a test group (TG) or a control group (CG). Standard acupuncture treatment included electroacupuncture, body acupuncture and ear acupressure, and was applied ten times

during 3–4 weeks either at presumed anti-pain acupoints (TG) or at sham points (CG). A physician measured the pressure pain threshold (PPT) at 28 trigger points in the neck and shoulder region with algometry before the first treatment, after the last one and 6 months after the treatments. Questionnaires on muscle pain and headache were completed before each treatment, just after the course, and six months and three years later.

Results

- During the treatment period, the intensity and frequency of pain, and the degree of headache fell more for TG than for CG ($P_b \leq 0.04$; $P_b = 0.02$).
- Three years after the treatments, TG still reported less pain than before the treatments ($P_w < 0.001$), contrary to what CG did ($P_b < 0.04$). And the acupuncture effect on the degree of headache lasted for TG ($P_w < 0.001$), while for CG headache was back to the pre-treatment level ($P_b < 0.001$).
- The value of PPT of some muscles rose during the treatments for TG and remained higher 6 months after the treatments ($P_w < 0.05$), which contrasts the situation for CG.

Conclusions Acupuncture treatment may reduce chronic pain in the neck and shoulders, and related headache. The effect lasted at least three years.

4.4 Paper IV

Effect of intensive acupuncture on pain-related social and psychological variables for women with chronic neck and shoulder pain – an RCT with six month and three year follow up. ***Acupunt Med*** 2005; 23(2):52-61

Objectives To examine whether acupuncture treatment can improve several social and psychological variables for women with chronic pain in the neck and shoulders, and to examine whether possible effects are long-lasting.

Methods Twenty-four female office workers (47±9 years old, mean±SD) who had had neck and shoulder pains for 12±9 years were randomly assigned to a test group (TG) or a control

group (CG). Intensive acupuncture treatment was applied ten times during 3–4 weeks either at presumed anti-pain acupoints (TG) or at sham points (CG). Questionnaires for social and psychological variables were completed before each treatment, just after the course, and six months and three years later.

Results

- The pain-related activity impairment at work was less in the TG than the CG by the end of treatment and at 3 years follow-up ($P_b<0.04$).
- The pain-related activity impairment at home for TG was less at 3 years follow-up than before the treatments ($P_w<0.004$), while CG fell back to the pre-treatment level ($P_b<0.03$).
- There were significant differences between two groups for the pain-related variables, such as quality of sleep, anxiety, depression and satisfaction with life after the treatments ($P_b<0.05$). At 6 months and 3 years follow-ups the TG showed further improvements in most pain-related variables and was again significantly different from the CG.

Conclusions Acupuncture treatment can improve the activity at work and several relevant social and psychological variables for women with chronic pain in the neck and shoulders. The effect may last for at least three years. Hypothetically, acupuncture may reduce the chronic pain by breaking the vicious circles involving e.g. pain, depression and pain-related activity impairment.

5 DISCUSSION

Oh, East is East and West is West, and never the twain shall meet.

... ...

But there is neither East nor West, Border, nor Breed, nor Birth,

When two strong men stand face to face, tho' they come from the ends of the earth!

Rudyard Kipling, *The Ballad of East and West*

5.1 Methodological considerations

5.1.1 Random error, power calculation

Study A had one major outcome measure: daily cigarettes consumption, with a fairly well established distribution (standard deviation). Unlike this, Study B had several different important outcome measures, and none of them had well established distributions, implying that it would be very difficult to carry out formal power tests in advance. The number of subjects in Study B was somewhat less than that in Study A, but also for Study B a moderate effect with a moderate variability would most probably be detected by our approach. In any instance, after a study has been completed, considerations of power have little interest unless one wants to understand why an intervention did not lead to statistically significant results, and would accordingly not be of major interest for the present studies.

5.1.2 Sample selection

5.1.2.1 Subjects' characteristics

Selection bias is defined as an error due to a systematic difference between the characteristics of the individuals studied and not studied (149). The main requirements for including subjects to Study A was that "the subjects should have at least five years of regular smoking, and an average tobacco consumption of 10-30 cigarettes per day during the last year". In order to avoid *sample bias*, which may be caused by failure to choose an appropriate sample, the extreme light- or heavy-smokers were excluded (150). A total of 48 smokers were included. One female 'light smoker', i.e. smoking 1-2 cigarettes per day, and one male heavy smoker consuming 40-45 cigarettes daily were excluded. The requirements for including subjects to Study B referred to the standard method (151), when defining "chronic" pain in the neck and shoulder region. Since both studies were based on small sample sizes by randomization, it is important to keep the subjects more homogeneous by using restrictive inclusion and exclusion criteria (152).

5.1.2.2 Drop-outs and missing data in the follow-up studies

There were no drop-outs in Study B, neither during the acupuncture treatment period nor in 6 months and 3 years follow-ups, except for one subject in CG who did not appear for blood sample collections and algometric measurements.

In Study A, there were two subjects in CG who dropped out during the early treatment period, presumably due to lack of motivation. Several missing data appeared in the follow-up studies, particularly in the five years' long-term follow-up. Losing subjects during follow-up is a major concern in cohort studies, becoming progressively more important with time (153, 154). Anyhow, the reasons for withdrawal were loss of availability due to migration, change of jobs, or even death. Fortunately, in the present studies we found no systematic difference between the drop-out subjects and those who completed the follow-up studies on smoking characteristics or in other parameters like age. Therefore, we assume that there is no *drop-out bias* and *missing data bias.* Rather, the missing data in the present studies are more likely random effects that do not influence the validity of the study.

5.1.3 Acupuncture treatments, reliability and validity

5.1.3.1 Standardized acupuncture treatment

Acupuncture treatment for TG and CG in both studies was standardized on number of acupuncture points used, depth and duration of needle inserted, and sessions of treatments given. Based on the principles of TCM, it could be argued that particular treatments should be given for each patient. This is especially relevant in Study B where chronic pain was located in different places in the neck and the shoulders of the patients. In the present study the intention was to carry out as similar treatments as possible within and between each of the TG and CG, with reference to the principle of blindness and control, i.e. the subjects should not be able to distinguish between true and sham or placebo treatment.

5.1.3.2 Intensive acupuncture treatment

Clinical experience from China suggests that acupuncture treatments should be given at least every second day, and as a minimum of ten sessions for one course. Hundreds of years ago Yang pointed out that treatments should be applied every second day in order to receive optimal effect (135). Ma (155) emphasized that acupuncture treatment should be given every day or every second day, and a minimum of 7–10 sessions should be included in one course for treating chronic pain or insomnia. Some Western researchers also reported that several treatments are needed to obtain an effect (127, 156). Additionally, the tradition of TCM suggests that an adequate acupuncture treatment regimen should include several acupoints, a combination of different acupuncture techniques, and that enough time of stimulation should be used during each session (7, 136). Therefore acupuncture treatments in both studies in the thesis were a combination of three different acupuncture techniques, used at several acupoints, and carried out at 6-10 sessions (more details will be discussed in Section 5.4.1).

5.1.3.3 De Qi sensation

According to the theory of TCM, it is essential for a patient to get De Qi during treatment in order to provide a more positive effect (4, 7, 157). De Qi is a typical sensation that the patient feels such as numbness, pressure, heaviness, soreness, cold or heat, when the needles are inserted and retained in acupuncture points. And De Qi is actually an individual experience of the Qi phenomenon and differs between patients, technique of the acupuncturist, and places of

needle insertion (136, 158-160). It is believed that De Qi sensation is received only in real acupoints. In our treatments, irrespective of group (TG or CG), each needle was given manual stimulation, i.e. rotated, every 5 minutes when it was in the body, which is considered to be one of the most important techniques to manipulate De Qi during acupuncture treatment (136, 160-162). In the present study, however, we did not ask whether the subjects received De Qi, because we had to keep communication equal for all subjects under treatment. Additionally, it is not known whether De Qi can be obtained by sham or placebo acupuncture. On the other hand, the treatments were given by an experienced acupuncturist (the author of the Thesis). Therefore, it is assumed that the subjects in TG did receive complete acupuncture treatment.

5.1.3.4 Acupuncture practitioner

As mentioned above the acupuncture treatment was carried out by the author of this thesis, who is educated in TCM in Beijing, and who has 15 years of experiences with acupuncture in clinics in China and Norway. Besides clinical work, she has more than 10 years of experience in acupuncture research. In spite of this, it can not be ruled out that there was *information bias* in the study, since she was the only one to carry out the acupuncture treatments, and was aware of study design. More details about this point are discussed in the Papers, and in the Section *5.1.4.3* and *5.4.3.*

5.1.4 Outcome measurements; reliability and validity

We have used three instruments to measure the outcomes, i.e. self-reported questionnaires, clinical observations, and measurements of biochemical variables.

5.1.4.1 Questionnaire

Most of the questions in the studies were based upon previous standard questionnaires, but several questions were constructed for this study, e.g. taste of tobacco and desire for smoking, as well as degree of tiredness. However, independent measurements, so called *criterion validity or the gold standard* were the most obvious way to appraise the validity and strengthen the questionnaires' results (163). In Study A, the concentration of serum cotinine and thiocyanate correlated positively with the reported tobacco consumption at baseline, as well as after the last treatment, and the 8 month follow-up, and then the tobacco consumption

correlated with taste of tobacco and desire to smoke. In Study B the results of PPT measures supported the observed effects on pain relief.

Concerning the *content validity* of the questionnaire that we constructed, several aspects of the same variable were measured, e.g. questions were addressed on the subjects' intensity of chronic pain by different ways, using VAS and Categorical scales. Moreover, we had different time axes to assess pain, i.e. last month, last week and at present (163, 164).

Questionnaires of studies were filled in by the subjects alone to avoid possible *obsequiousness bias*, defined as the phenomenon that subjects may alter their response to fit what they think the investigator wants (149). Subjects were asked to complete the questionnaire before each acupuncture treatment to reduce possible *response bias* and improving the reliability and validity of information received (165, 166).

The length of the time period in question is an important issue when considering *recall bias* (164, 167). Although most data collected in the studies are at "right now" time, or last week, some data of the cohort study used longer time axis, i.e. last six months. And some questions used baseline as reference to address possible changes in long-term follow-ups. Since it can be doubtful whether the subjects could remember at the follow-ups, i.e. how tobacco tasted before the treatment, the results should be interpreted with caution.

Questions related to the subjects' social and psychological status in Study B used a VAS-scale instead of standard Q-36, because it was difficult for the subjects to fill in such a long questionnaire before each treatment.

5.1.4.2 Physio-biochemical or clinical examination

In Study A, concentrations of serum cotinine and thiocyanate were included. These variables are standard measurements and widely used to assess smoking habits (142, 143). The measurements of plasma fibrinogen and TBARS are also widely used methods (146, 168). Four experienced technicians from three different institutions carried out the measurements, and all were unaware of the study design. Therefore, we assumed the measurements were reliable.

Measuring PPT by algometry is one of the main clinical and standard methods to assess patients' pain status, since pain is based on the individual's experience. In Study B, the medical doctor who carried out this part of measurement was unaware whether each subject belonged to the TG or CG until after the 3 years follow-up finished.

5.1.4.3 Further formal methodological issues

As this topic mentioned in all Papers, the present study was single-blind, since the acupuncturist had to know the observed treatment procedure. A possible bias due to this limitation formally can not be ruled out. But we have considered several points below, in order to use the maximum degree of blindness that is possible (152).

Randomization: The subjects were randomly divided into two groups referred to as a *test group* (TG) and a *control group* (CG) by drawing of lots with replacement. The general characteristic of the subjects in TG and CG for both studies were balanced.

Treatment indistinguishable: The treatment for control group in Study A was sham acupuncture, and in Study B was placebo acupuncture. Except for the acupoints (real or sham/placebo), there was no difference in the treatment procedure between TG and CG with respect to the number of points applied in the body, the depth and duration of needle insertion, and verbal or non-verbal communications with the acupuncturist. In our opinion, we consider that the true and sham (placebo) acupuncture treatments appeared generally indistinguishable for the subjects of TG and CG.

Physiologic measurements: Collection of blood samples and physiologic measurements for Study A and B were carried out fully independently and blinded.

Clinical measurements: In Study B, the physician who carried out clinical examination and measured of PPT on subjects was unaware of what kind of treatment each subject received. Moreover, until the 3 years follow-up had been completed, the acupuncturist was unaware of the results of the algometric measurements. So this part of the Study B was double-blind.

5.2 Discussion of main findings in Study A

5.2.1 Short- and long-term effects of acupuncture for smoking reduction and cessation

It is difficult to compare the results in the present thesis with others because the studies differ in experimental design. Anyhow, the superior effect of acupuncture on smoking cessation and reduction for TG right after treatment, which is presented in Paper I, are in line with a number of previous studies (47, 49, 51, 53-56), and are confirmed by several randomized controlled trials later (50, 60).

A number of acupuncture trials have addressed possible long-term effects of acupuncture on smoking cessation during the last 30 years. However, the length of the follow-up period in different experiments varied from 14 days to 4 years, and the results are quite inconsistent.

Results for the TG in the present Study A suggest a maintained reduction of smoking during the 8 months follow-up period. This is in line with other studies that have shown a positive effect of acupuncture on smoking withdrawal six months and one year after the intervention (48, 50-53, 57, 59, 60). Paper II presented no difference between the follow-up results 8 months and 5 years after the last treatment for each group. Accordingly, there might have been a more sustained acupuncture effect also in the studies referred to above. It is, however, difficult to compare directly the results of 5 years follow-up with the others, since none of the previous studies had 5 years cohort data in their trials.

5.2.2 The acupoints used for smoking cessation

One of the interesting questions in the thesis was to clarify whether some acupoints are more effective than others for smoking cessation. This was accomplished by comparing acupuncture at real acupoints with sham acupuncture (i.e. one assumed to be anti-smoking acupoints, while the other was not, see Section 3.3.2 for details). The significant differences obtained between the two groups as regards smoking cessation, taste of tobacco and desire to smoke after acupuncture, as demonstrated after 5 years, strongly suggest that different effect on smoking cessation do exist in two sets of acupoint applied in Study A. The results seem to be in accordance with some previous trials that focused especially on differences in the effect of acupuncture on real and sham/placebo acupoints on smoking withdrawal (50, 60).

There may have been some placebo effects in Study A since the CG, which was given sham acupuncture, had to some extent reduced cigarette consumption, and also experienced a decrease as regards taste of tobacco and desire to smoke. On the other hand, the acupuncture effect was more pronounced on the TG, as observed on all variables and at all observation points of the study. And, as illustrated in the 8 months follow-up study: while the TG presented a lasting effect of treatment, for the CG the taste of tobacco and desire to smoke fell back to, or even worsened as compared with the pre-treatment level (Paper II).

5.2.3 Taste of tobacco and desire to smoke

To our knowledge, we were the first to examine quantitatively acupuncture in relation to the subjects' taste of tobacco and their desire to smoke. This was accomplished using a VAS-scale (Paper I, II). However, some previous studies have mentioned that the subjects' desire to smoke was reduced by acupuncture, and that tobacco no longer tasted as good as before the acupuncture treatment (47, 48, 51, 57, 60, 65).

Interestingly, others have adopted our method of analyzing the taste of tobacco and desire to smoke (169). The findings from a recent RCT experiment support our results in Paper I and II as regards the changes of the taste of tobacco and the desire to smoke after the acupuncture treatment. Thus, Kang and colleagues (169) reported that the active (treatment) group experienced a significant decrease in the taste of tobacco and desire to smoke after 4 acupuncture sessions, although no differences were observed on cigarette smoking reduction and cessation between active and control groups.

Several studies of CAM treatment have also focused on the treatment effect on smoking withdrawal symptom, i.e. desire to smoke, and anxiety (41, 43). Applying self-massage to the hand or ear, Hernandez-Reif and colleagues (40) found a reduction in the smoking craving intensity, as measured by Likert scale and VAS scale. The effect was found both in the active and control group. Their results seem to be in line with ours and would suggest that a decrease of the subjects' taste of tobacco and desire to smoke might serve to facilitate smoking reduction.

5.3 Discussion of main findings in Study B

5.3.1 Short- and long-term effects of acupuncture on pain reduction

5.3.1.1 Reduction of chronic neck and shoulder pain

The effectiveness of acupuncture for reducing chronic neck and shoulder pain in the TG immediately post-treatment, as described in Paper III, is in accordance with the results reported by Peng (106), and also with those of Nabeta and Kawakita (105). Moreover, our results showing that acupuncture can reduce pain are in agreement with several other previous studies examining the influence of acupuncture for pain relief on one location, e.g. on the neck or shoulders (111, 112, 127, 130, 170-173). Furthermore, some recent studies have also confirmed that acupuncture may reduce the subjects' chronic musculoskeletal pain immediately after treatment (110, 114).

5.3.1.2 Reduction of chronic neck and shoulder pain-related headache

All subjects of Study B suffered additionally chronic neck and shoulder pain-related headache. Conceivably, chronic musculoskeletal pain is often associated with other physical impairment. According to the theories of TCM, the various components of a chronic pain syndrome should not be treated separately. Rather, the whole syndrome should be treated (17, 21, 174).

The results obtained in Paper III showed that the degree of chronic pain-related headache decreased significantly for the TG right after treatment. Our results are in line with other previous findings concerning the effect of acupuncture on neck pain-associated headache (120, 122), and are also supported by two more recent studies in which acupuncture was used for chronic headache (123, 125).

5.3.1.3 Long-term effect of acupuncture on chronic pain reduction

As mentioned in the Background chapter (Section 1.3.3), most of the studies on acupuncture for chronic pain relief have followed their subjects for just some months or less. In Paper III, we pointed out that the significant differences in pain intensity, pain frequency, and degree of headache between the test and control group disappeared at 6 months after the treatment, but reappeared at 3 years follow-up. This observation would seem to be a reminder that one

should be very cautious when drawing the conclusion of no benefit from acupuncture on chronic pain based upon short-term previous studies, i.e. studies that failed to show different effects between true acupuncture and sham treatment 6 months after treatment, or even after a shorter follow-up period (109, 117, 118).

However, the present finding of a long-term, sustained beneficial effect of acupuncture upon chronic pain in the neck and shoulders, and even on the degree of headache, would seem to be an extension of the results of Junnila (129), who reported a lasting, pain relieving effect in 26% of the subjects when examined at 2 years after the acupuncture treatment.

5.3.2 Short- and long-term effects of acupuncture for chronic musculoskeletal pain-related social and psychological variables

The third research question in the thesis is to explore whether acupuncture may have effect on pain-related social and psychological variables in women with chronic pain in the neck and shoulders. As observed in Paper IV, the score for pain-related activity impairment at work improved significantly more in TG than in CG right after the intervention. This result is in line with some previous studies examining the effect of acupuncture on chronic neck pain (127, 129, 130) and also on chronic low back pain (131, 132).

In TCM theory, one of the most important benefits for all kind of sickness is to improve patient's quality of sleep, because the presence of sleep disturbances implies always a deficiency of kidney-energy and/or excess of heart-energy. Kidney and heart are two most essential organs to balance the energy of Yin and Yang in the body (174). The superior acupuncture effect on quality of sleep in the treatment group (Study B) is consistent with the results of Strauss (120) and Sator-Katzenschlager et al. (130), who examined the influence of acupuncture on chronic neck pain. Additionally, some authors have considered that there is a significant better quality of sleep after acupuncture in subjects with chronic low back pain (131, 132).

In Paper IV, we have extended the studies of acupuncture upon pain-related symptoms; our study shows several positive changes of psychological factors in subjects receiving acupuncture treatment, such as reduced anxiety, irritability, depression, and increased

satisfaction with life. These findings coincide with the results by Sator-Katzenschlager and colleagues, who found a positive influence on psychological well being after ear electro-acupuncture treatment both on patients with chronic neck pain (130) and chronic low back pain (131).

Paper IV presents a possible time-related pattern of the acupuncture effect on chronic neck and shoulder pain-related social and psychological variables. The differences between the test and control groups of most variables observed in Paper IV increased in the follow-up periods. So far, to our knowledge there is no other study that we can compare our results with as regards positive long-term effects of acupuncture on chronic pain-related social and psychological variables. Accordingly, our data on the long-term acupuncture effects seem to be novel.

5.4 Study design

5.4.1 Acupuncture dose

Formulation of an acupuncture receipt is based on several TCM theories, i.e. the Jing-Luo theory, the Yin-Yang theory, and the Zang-Fu principles. The treatment is usually specific for each patient and strongly influenced by the symptoms in question. Therefore, only recommended rules and doses of treatments have been applied for different conditions both in ancient and modern literature on TCM. However, this special requirement produces a difficulty for Western acupuncture researchers with regard to choosing the appropriate acupuncture treatment type and dose, when they carry out an RCT with standardized acupuncture.

A number of articles have emphasized that it is crucial to perform acupuncture trials with high methodological quality of Western scientific standards, e.g. having large sample sizes, objective validation, randomization, long-term follow-up and so on (101, 175, 176). On the other hand, it is also essential that the acupuncture treatment itself, applied in the study, should be designed and carried out with the appropriate dose according to the principles of acupuncture theory of TCM. It would seem that this latter important issue, so far, has not be paid enough attention, and is not adequately discussed in the literature.

Very few authors have touched the topic of acupuncture dose (177, 178), Shi and his colleagues observed the acupuncture effects on different disorders, e.g. stroke or asthma. They summarized that an optimal interval between two acupuncture treatments is 3-6 hours, and an optimal time for needling on each acupoints applied in treatment is 1-3 minutes (178). On the basis of many years' acupuncture practice and research experience, in Table 1 the author of this thesis sums up the main elements that might influence the acupuncture dose during the treatment, and the regular doses given in practice, since this kind of information is limited in the literature.

Ancient principles of TCM suggest that it should involve needling (acupuncture), Tui Na (Chinese medical massage) and Ju Liao (moxibustion) together to produce a better result (19). A combination of 2–3 different treatments including electroacupuncture, classical acupuncture, ear acupuncture, ear acupressure and laser acupuncture are regularly used in current acupuncture practice in China. From my experience in clinical practice, combining different acupuncture techniques in the treatment often gave improved results. As discussed above (Section 5.1.3.2), the doses of treatment applied in the present thesis, both in Study A and B, were intensive. Three acupuncture techniques were used in each session, there were many acupoints, each treatment was of adequate duration and intervals between each session were short.

The key acupoints, i.e. *confluence acupoints* or *Wushu (distal) acupoints* of meridian, have usually specific functions in treatment (135, 136, 179, 180). Thus, Lieque (LU 7), Kongzui (LU 6) are chosen for producing a strengthening effect in Study A, and Fengmen (BL 12), Hegu (LI 4) for obtaining a similar effect in Study B. This basic factors influencing the acupuncture treatment, as well as the different types and intervals of needle rotation, e.g. the *tonifying* or *sedating manual needling*, should be taken more into consideration in future acupuncture research.

Table 1. Common determinants and amounts of acupuncture dose*

Common used techniques	Classic acupuncture Ear acupuncture Acupressure Electroacupuncture Laser acupuncture Trigger point acupuncture Indwelling ear acupuncture Combination of 2–3 techniques
Number of acupoint	3–25
Type of acupoint	General point, local point, distal point, end point, influential point, confluence point
Size of needle	Diameter: 0.1 mm–0.4 mm Length: 10 mm–75 mm
Insert depth of needle	2–40 mm
Type of needle stimulation	Manual stimulation (superficial, deep, neutral, tonifying, sedating) Electrical stimulation
Duration of manual needle stimulation	15 sec–3 min
Interval of manual needle stimulation	1 time/20 min–1 time/3 min
Duration of each session	5–50 min
Interval of sessions	1 session/week–2 sessions/day
Session of treatment	3–10 sessions are one course; 1– 5 courses

* The components in the table are used commonly in practice, and most of the techniques can be applied on body or/and ear acupoints.

Adequate treatment, as obtained by extending the duration of each session and also by increasing the frequency of sessions, is another major issue. In Study A, the reduction of cigarette consumption was observed after the first session of treatment for both groups, that is by 59% (TG) and 30% (CG). And for TG, a significant reduction was registered both after the second and after the fourth session, when comparing with the previous session, but not for CG (Paper I, II). In Study B, although each subject received ten intensive acupuncture treatments, given as three sessions per week, the effect on intensity of pain and quality of sleep did not differ between the two groups until six and eight sessions were completed. The same

improvement pattern was shown on pain-related psychological variables (Paper III, IV). It appears that a typical program of acupuncture treatment for chronic pain should continue during several weeks. Most often, patients obtain increasing periods of relief with each successive treatment. Repeated treatments are usually performed weekly for 6 weeks, or twice weekly for 3 weeks (181).

5.4.2 Simplified acupuncture treatment method in Western acupuncture research

Many of the studies referred to above seem to have carried out simplified treatment with too low acupuncture dose, i.e. using fewer than 3 acupuncture points, shorter than 10 minutes stimulation in each session, 1-3 sessions for the whole course, and a lower frequency than once weekly. Accordingly, it would appear that a low treatment dose is the main reason that some authors were unable to detect any effect of acupuncture on smoking cessation or on chronic pain reduction. This research problem exists generally in Western acupuncture research for many studies and for different disorders. Some authors have pointed out that the simplified treatment even could be one of the reasons that lead to a gap between studies showing no efficacy of CAM and reports of considerable clinical benefit from patients and practitioners (182).

In addition, it is essential to evaluate an optimal method of acupuncture treatment in TCM with how much *overall effectiveness* the patients obtain. Several reports have been aware of this issue of acupuncture treatment (84, 132, 183-186). Thus, in addition to get positive effects of acupuncture on the specific problem approached, the patients should also receive some beneficial influences on their general health, e.g. better quality of sleep, more daily activities, better moods etc. (13, 21, 174). It would be more difficult for the patient to receive the overall effectiveness in studies applying only simplified acupuncture treatment, because their cumulative effect of treatment may not reach the relevant level.

5.4.3 Possible placebo effect and value of long time follow-up

Placebo effect is an expression of the subject's belief or expectancy that the treatment is beneficial (149), and it exists in different experiments and is far from specific. In studies on chronic pain, the fraction of placebo responders (at least 50% pain relief) has varied from 18%

to 36% (165). Placebo effect has been one of the crucial points in the studies of acupuncture effect, since it is difficult to perform RCT with double-blindness.

The control group in Study B experienced a placebo effect; right after receiving placebo acupuncture only, subjects in CG also experienced that chronic pain was reduced and pain-related social and psychological variables improved. However, these effects were small compared with those of the TG. Furthermore, in CG the effects were temporary, i.e. most of them had disappeared at 3 years follow-up. This finding emphasizes the importance of performing follow-up several years after the treatment in order to identify any real, long-lasting effect of acupuncture. It should be point out that long-lasting effects are essential also for the patients. More details on this point are given in Paper IV.

In addition, a placebo effect can be produced by good physician-patient interaction (165). The acupuncturist's expectations and the subjects' perception of the expectation may also induce the placebo effect. As mentioned in the Papers I-IV, the author of this thesis has carried out all the acupuncture treatments in the Study A and B. Thus, a possible bias can not be ignored, even though she tried hard to communicate with all subjects as evenly as possible, whether they belonged to the control or test group. Additionally, the subjects' desire to quit smoking (Study A) and longing for reducing of pain (Study B) might partly be attributed to a placebo influence.

5.5 Correlations and models for possible mechanisms of action

The limiting factor as regards the validity of studies on acupuncture is the lack of independent biologic markers which could be controls of the self-reported data (designated as "the gold standard" in this kind of experiment). The positive correlations provided in Study A between subjects' smoking-related blood variables, especially the concentration of serum cotinine, and self reported smoking habits (Paper II) is in accordance with another study which used urinary cotinine to assess the outcome (50).

Furthermore, a positive correlation appeared between the taste of tobacco, desire to smoke and the subjects' reported cigarette consumption (Paper II). Based upon these results we proposed a possible model for the effect of acupuncture upon smoking reduction (see Figure 5). Thus,

by reducing the taste of tobacco, there is a reduced desire of smoking, and hence reduced smoking. Theoretically, acupuncture could reduce the desire of smoking without affecting the taste. More details are given in Paper II.

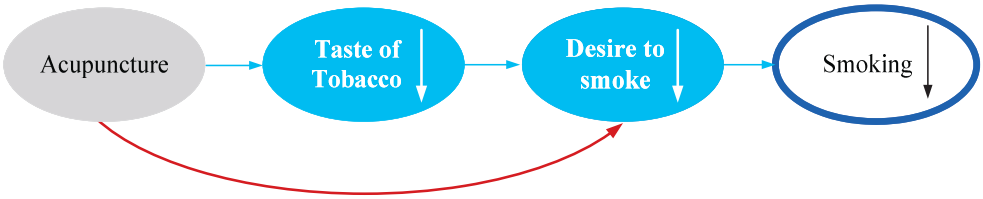


Figure 5. Proposed model for effect of acupuncture on smoking cessation and reduction

In Study B, we have also proposed a model to illustrate how acupuncture may influence the subject, with regard to pain relief (Figure 6). The model is based upon correlation found among the variables in the study. Thus, the changes in the experience of pain correlated with changes in the subjects' daily activity, with their changes in the degree of depression, anxiety and irritability, with their satisfaction with life, and also with the quality of sleep (more details are given in Paper IV). It is possible, however, that the primary effect of acupuncture in depressed subjects with chronic pain is to relieve depression, with subsequent pain relief and increased activity.

Some of the correlation presented in Paper IV are qualitatively in line with a cohort study by Kukuk and co-workers (133) on chronic low back pain. Their study showed positive correlations between the improvement in pain tolerability post-treatment, subjects' depression score and the pain-related functional impairment.

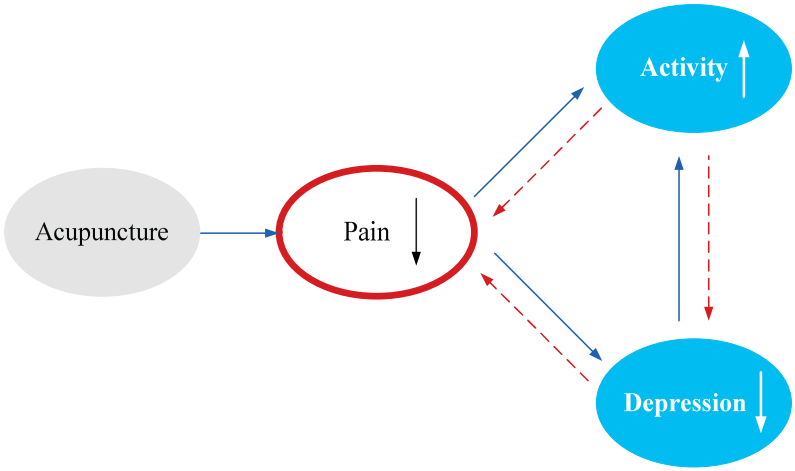


Figure 6. Proposed model for the effect of acupuncture on chronic pain

To explore detailed mechanisms underlying the acupuncture effect is not the main concern in the present thesis. Both of the included studies were clinical trials. We would, however, assume that complex neuro-physiological and -psychological changes are involved to explain the influence of acupuncture on smoking reduction, as well as on the relief of chronic pain.

It is believed that a penetrating acupuncture needle stimulates a sensory receptor inside the muscle, which sends impulses to the spinal cord and then activates three centres (spinal cord, midbrain, and hypothalamus-pituitary) to release transmitter chemicals, e.g. endorphins or monoamines, which causes the effect of acupuncture (6, 187, 188). Furthermore, it has been shown that low-frequency (2-4 Hz), high intensity stimulation of electro-acupuncture works through the endorphin system and acts in all three centres, and produces the effect with slower onset but longer duration than high-frequency (>50 Hz), low intensity electro-needling does. Also, its effects are cumulative, becoming increasingly strong after several treatments (21, 189-191).

Both studies in the thesis used low-frequency (3 Hz), high intensity stimulation of electro-acupuncture. The adequate dose of acupuncture emphasized in the preceding section 5.4 is obtained by applying the treatment several times. Hypothetically, it would appear that one of the mechanisms involved is that the spinal cord, midbrain, hypothalamus-pituitary, and even cerebral cortex need time to “learn” and synthesize the cumulative signals from each

sequential repeated treatment, so as to subsequently be able to release enough transmitters to break the physiological and psychological vicious circles presumed to be involved in smoking or chronic pain (192, 193).

5.6 Generalization

None of subjects in Study A smoked more than 30 cigarettes daily, since such heavy smokers did not comply with the inclusion criteria. Accordingly, the positive result of acupuncture on smoking reduction and withdrawal observed in this thesis can not be extended to include heavy smokers consuming over 30 cigarettes per day. A limitation is also the relatively small sample size, i.e. more studies are required to confirm that the observed acupuncture effects on smoking reduction are in fact valid for smokers in general.

In Study B, we have examined only one sample of sedentary female workers who with chronic neck and shoulder pain. Therefore, the subjects in Study B may not be representative of all people with chronic neck and shoulder pain. In addition, the sample size of this study is small, so that the observed positive results of acupuncture on chronic pain in this thesis may not necessarily be generalized.

6 CONCLUSIONS

This Thesis has focused on two major health problems in modern society: smoking and chronic musculoskeletal pain. Both are difficult to prevent, and there seems to be no effective treatment in traditional medicine.

The results obtained in this work suggest, that acupuncture can reduce cigarette smoking, and also to relieve chronic musculoskeletal pain.

More specifically, the main conclusions from this thesis can be summarized as follows:

- Appropriate acupuncture treatment may help motivated smokers to reduce smoking, or even quit smoking completely.
- Different acupoints appear to have different effects on smoking reduction.
- Acupuncture may reduce the taste of tobacco and the desire to smoke, thereby possibly reducing smoking.
- Appropriate acupuncture treatment may reduce chronic pain in the neck and shoulders, and related headache.
- In patients with chronic pain in the neck and shoulders appropriate acupuncture may improve activity at work, and positively influence several relevant social and psychological variables.
- Through reducing musculoskeletal pain, acupuncture may improve daily activity and reduce depression.
- The positive effect of acupuncture on smoking cessation and reduction, and on chronic neck and shoulder pain can be long lasting.

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